Diabetic Retinopathy
A Guide for G.P.s

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Disclosures: Consultant for Novartis, Bayer, Abbott, Allergan

Management of Diabetic Retinopathy

We tell patients - these are the strategies to maintain good vision during life with diabetes?

• Maintain optimal or near-optimal control of blood glucose, blood pressure and lipids
• Undertake to attend regular ophthalmic exams from diagnosis, at least 2-yearly then more frequently once retinopathy is found, as recommended
• Attend without delay if vision changes in either or both eyes; do regular self-testing
• Trust your general practitioner and ophthalmologist to give you good advice and be willing to take this advice

Use NHMRC guidelines

All people with diabetes need an eye exam at diagnosis, then at least every 2 years – indig/other 1Y

If minimal or mild NP (non-proliferative) DR see yearly – optometrist or ophthalmologist

Alternately, GP’s can screen – new Medicare item Nos. (12325, 12326) – can be used each 2Y (~$50) 1Y Indig; need VA checked; if <6/12 need to refer
If mod/severe NPDR: rev 3-6 mo. Ophth
If VTDR then treat as appropriate
How to manage DR?

1st understand the biology

- DR is a complication of a systemic disease
  - Ocular treatment is not sufficient
- DR is a vascular disease of the small blood vessels
  - Surgery is not the cure

2nd understand the natural history

- DR severity
  - None
  - Mild NPDR: Microaneurysms only
  - Moderate NPDR: Microaneurysms & Hemorrhage
  - Severe NPDR: 4 quadrants of Hemorrhage
  - Proliferative DR: New vessels or vitreous hemorrhage

- Diabetic macular edema (DME)
  - None
    - Non-Centre-involving: Away from fovea center
    - Center-involving: Involving fovea center 1mm diameter

Treatment for severe NPDR/PDR and/or DME

Principles of Management of DR

Primary Prevention
- Prevent diabetes
- Systemic control

Secondary Prevention
- DR Screening
- Systemic control

Tertiary Prevention
- Ocular Treatment

#1. Glycemic control demonstrated for T1DM...


Intensive glucose control reduces onset of DR by 75%
...but reduces progression of DR by only 50%

...primary prevention has the strongest effect and reduces risk of DR by 75%; secondary prevention is less effective...
...takes >3 years before beneficial effects are seen
…early good glycemic control has long-term benefits ("metabolic memory") → epigenetic modifications…

…however, glycemic control may not be as effective in T2DM

Hemmingson. BMJ 2011

<table>
<thead>
<tr>
<th>Study</th>
<th>Intensive control</th>
<th>Conventional control</th>
<th>Risk ratio (metabolic risk, random) (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (metabolic risk, random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 1998</td>
<td>25/139</td>
<td>25/139</td>
<td>1.31 (0.99 to 1.73)</td>
<td>21.2</td>
<td>7.9 (0.99 to 6.49)</td>
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<tr>
<td>VA CGDR 1993</td>
<td>22/75</td>
<td>22/75</td>
<td>7.76 (2.43 to 26.64)</td>
<td>21.1</td>
<td>11.9 (0.91 to 12.4)</td>
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<tr>
<td>Kumaresan 2000</td>
<td>12/135</td>
<td>17/135</td>
<td>15.6 (4.58 to 5.04)</td>
<td>31.0</td>
<td>15.9 (0.95 to 22.0)</td>
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<tr>
<td>ACCORD 2001</td>
<td>12/139</td>
<td>17/139</td>
<td>17.1 (4.56 to 65.15)</td>
<td>4.0</td>
<td>16.1 (0.61 to 1.05)</td>
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<tr>
<td>ADVANCE 2000</td>
<td>99/791</td>
<td>79/791</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VADT 2009</td>
<td>134/799</td>
<td>134/799</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>74/6573</td>
<td>660/4618</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for heterogeneity: e0.004, p=0.1456.</td>
<td></td>
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<tr>
<td>Test for overall effect: p=0.009, p=0.053.</td>
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</tbody>
</table>

...Intensive glycemic control reduces risk of DR by 20% in T2DM vs 75% in T1DM...

#2...for T2DM, BP may be equally or more important

UK Prospective Diabetes Study (UKPDS). Lancet 1998; 352:837-853

"Tight" BP control associated with lower risk of

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>% Lowering</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy progression (7.5 yr)</td>
<td>34</td>
<td>0.004</td>
</tr>
<tr>
<td>Photocoagulation for CSME</td>
<td>42</td>
<td>0.016</td>
</tr>
<tr>
<td>Retinal photocoagulation</td>
<td>35</td>
<td>0.023</td>
</tr>
<tr>
<td>3-line decrease in vision</td>
<td>47</td>
<td>0.004</td>
</tr>
<tr>
<td>Blindness in one eye</td>
<td>24</td>
<td>0.046</td>
</tr>
<tr>
<td>Microalbuminuria (&gt;50 mg/L, 6 yr)</td>
<td>29</td>
<td>0.009</td>
</tr>
<tr>
<td>Gross albuminuria (&gt;300 mg/L, 6 yr)</td>
<td>39</td>
<td>0.061</td>
</tr>
</tbody>
</table>

"tight" glucose control vs "tight" BP control

However, BP control has been shown to be effective only in patients with T2DM with hypertension

#3. Lipids and DR

…link between "traditional" lipid measurements and DR is unclear

Fenofibrate reduced the progression of DR by 40% (relative risk reduction, \( p=0.006 \)) over 4 years.

**Fenofibrate prevents 1/3 of DR progression in patients with type 2 diabetes**

- Fenofibrate is a lipid-modifying agent used to reduce triglyceride levels and increase HDL-C.
- Two major studies have shown novel benefits of fenofibrate in DR that are not linked to its lipid-modifying effects:
  - In FIELD, early treatment with fenofibrate reduced the need for laser therapy for DR by 31%.
  - In ACCORD Eye, fenofibrate-simvastatin combination therapy reduced DR progression by 40% compared with simvastatin alone.
- Fenofibrate is indicated to reduce the progression of DR in patients with type 2 diabetes and existing DR.
- Now a TGA approved indication: ‘any diabetic retinopathy’

**How do we apply FIELD, ACCORD eye results?**

- 2 large RCTs now demonstrate reduced DR/PDR/ DME progression (by 30% to laser in FIELD) and by 40% (by 3 steps on the ETDRS scale in ACCORD-Eye) in T2DM taking fenofibrate.
- Fenofibrate is well established (30+ years), for diabetic dyslipidaemia, though this is not its mechanism of action in reducing DR progression？anti-VEGF, others.
- NNT for early NPDR was 14 in FIELD, 27 in ACCORD-Eye – both are in the ‘quite effective’ range.
- New guidelines for managing T2DM should reflect these data and consider a role for this agent – no other oral medications have shown this impact on DR.
- Fenofibrate should be recommended in patients with early DR, in letters to GP’s, physicians.
How do we apply FIELD, ACCORD eye results?

Ophthalmologists’ role

- Ophthalmologists should recommend GPs/physicians commence fenofibrate in patients with DR, explaining that:
  - Effect of fenofibrate on DR progression is unrelated to fasting lipid serum levels
  - No benefit on DR has been shown from statins
  - Fenofibrate is safe in terms of interactions with statins, and overall is extremely well tolerated

1 in 10 persons with diabetes had VTDR*

(*Severe DR including severe NPDR, PDR & DME)

Management of DME

For DME, management has evolved

New Management Paradigms
1. “Prevention of blindness” → Vision improvement
2. Laser → Anti-VEGF treatment

DME – Diabetes Retinopathy

Prevalence (95% CI) per 100 people with diabetes

Factors of Interest

<table>
<thead>
<tr>
<th>Gender</th>
<th>Race</th>
<th>DM Type</th>
<th>DM Duration</th>
<th>HbA1c</th>
<th>Blood Pressure</th>
<th>Cholesterol (TC)</th>
<th>Study Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Caucasian</td>
<td>T1</td>
<td>&lt; 10 yr</td>
<td>&lt;=7.0%</td>
<td>Normotensive</td>
<td>&lt;4 mmol/L</td>
<td>Pre-2000</td>
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<td>Female</td>
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<tr>
<td>Male</td>
<td>African-American</td>
<td>T2</td>
<td>10-&lt;20 yr</td>
<td>7.1-8.0%</td>
<td>Hypertensive</td>
<td>&gt;=4 mmol/L</td>
<td>Post-2000</td>
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<tr>
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For DME, management has evolved


Intravitreal steroids
Laser
Intravitreal anti-VEGF

Ranibizumab
Bevacizumab
Aflibercept

2000s

DA VINCI (2011)
Ranibizumab
Aflibercept

2010s

RISE (2012)
RIDE (2012)
RESTORE (2011)
VIVID
VISTA

"We hope to stabilize your vision and prevent blindness, but visual improvement is not possible"
ICO Guidelines 2017
Intra-vitreal Injections

1. Either topical or oral corticosteroids should be used on both the patient and surgeon to help prevent or minimize speech during the injection procedure and procedure.
2. Place the needle perpendicular to the ocular surface.
3. Apply pre-procedural drops to the ocular surface.
4. Apply pre-procedural drops to the ocular surface.
5. Apply pre-procedural drops to the conjunctival surface, including the intended injection site, at least 30 minutes before injection.
6. If additional anesthesia is requested, apply pre-procedural drops to the intended injection site immediately before injection (must use T4).
7. Insert the needle perpendicular to the ocular surface, 25 to 30 mm posterior to the limbus between the vertical and horizontal rectus muscles.

Female age 53, Diabetes 18 years   VA: 6/15, OCT 490 µm

Laser is not effective or possible in many eyes with DME

Diffuse DME → Poor response to laser

Center-involving DME with leakage at fovea → Laser not possible

Anti-VEGF therapy is now standard of care for DME

Ocular Anti-VEGF Therapy for Diabetic Retinopathy: Overview of Clinical Efficacy and Evolving Applications

Female age 53, Diabetes 18 years   VA: 6/15, OCT 490 µm
Anti-VEGF therapy is effective in improving vision and superior to laser…most trials for ranibizumab…

Anti-VEGF therapy is very intensive in 1st year…but less later

…challenge is "undertreatment" in 1st year but "overtreatment" in 2nd year onwards…

Anti-VEGF therapy works even in “chronic” DME previously treated with laser

…surprisingly good results for chronic DME…
Anti-VEGF agents may not be equal

- Allibecpt may be better in eyes with poor vision
- No difference in agents in eyes with good vision

Anti-VEGF for Diabetic Macular Oedema
- DME in around 5% of persons with known diabetes
- …esp Type 2, poor control, long undiagnosed D
- Around 7-8 injections needed Y1, 3-4 Y2, ?Y3
- Outcomes are excellent with adequate treatment
- Final VA depends on starting vision
- Many barriers to achieving this – e.g. out of pocket costs, anxiety, need for bilateral treatment
- Need to encourage patients to make course.

ICO Guidelines 2017

DME

Diabetic macular oedema (DME)
- Mild to moderate
- Moderate to severe
- Non-central involved
- Central involved DME
- VA better than 6/9 (20/30)
- VA 6/18 (20/30) or worse
- Focal or grid laser photocoagulation
- Treatment +/- Anti-VEGF therapy

Management of Severe PDR & PDR

Severe NPDR & PDR, Laser PRP remains 1st line treatment

Laser PRP has excellent long-term outcomes…
...but anti-VEGF has also been suggested to be useful in PDR...

Primary outcome: Adjusted difference in mean BCVA change was both non-inferior AND superior with aflibercept therapy compared to PRP at week 52

Male age 47, Diabetes 17 years, VA: R CF, L 6/9-rubeotic glaucoma R eye, iris NV's both eyes

Male age 47, Diabetes 17 years, VA: R CF, L 6/9-2 weeks after i/vit anti-VEGF, early PRP

Male aged 28 years, diabetes 12 years, VA: R 6/24, L 6/24

3 months after starting injections

3 weeks after presentation

DRCR.net Protocol S, CLARITY
Conclusions

1. DR is a **systemic microvascular** complication of diabetes
   ➔ Manage systemic control

2. **Glucose** and **BP control** are important in preventing progression of DR & vision loss

3. For center-involving DME, **anti-VEGF therapy** is effective in preventing vision loss and improving vision - barriers

4. For severe NPDR/PDR, laser PRP remains cost-effective treatment with good long-term outcomes

5. **Broad public health measures**, including education, raising awareness and uniform screening of DR is needed